Clinical Experience with Chlorpropamide

GEOFFREY WALKER, M.D., and LAURANCE W. KINSELL, M.D., Oakland

• Seventy-eight patients with mild diabetes were treated with chlorpropamide in doses up to 1 gm. daily. Eight showed primary failure to respond and two showed an initial but not a sustained response. Patients whose diabetes was of recent onset and who had not been treated with insulin or a sulfonylurea, required smaller doses than the remainder except for a group of patients who had been diabetic for more than 15 years.

The average dose for the 64 patients who took chlorpropamide for more than three months was 0.46 gm. per day. Serious side effects were uncommon and disappeared when the drug was stopped. One patient became jaundiced, one had a rash, and one showed granulocytopenia. Changes in liver function tests were seen in 17 out of 56 patients treated for more than three months and were correlated with the dosage of the drug and the duration of treatment.

CHLORPROPAMIDE (1-p-chlorobenzenesulfonyl 3-propylurea) was synthesized by McLamore and coworkers[10] during a systematic search for potent, long-acting, hypoglycemic sulfonylureas that were effective when given by mouth. It is marketed under the trade name of Diabinese.

This paper presents the results of a clinical trial of chlorpropamide conducted in the Diabetic Clinic at the Highland-Alameda County Hospital.

PATIENT SELECTION AND METHODS OF STUDY

Patients were selected for study only if they had noninsulin-dependent diabetes (that is, did not become ketotic when insulin was withheld) and were expected to cooperate in taking the drug and attending for review. They were seen at least once weekly during the first month and then approximately once monthly, depending on the adequacy of diabetic control. After a brief experiment with larger doses it was decided early in the trial to prescribe a standard initial dose of 250 mg. daily. The dose was subsequently adjusted according to postprandial blood sugar levels and the subjective well-being of the patients. The maximum dose was 1 gm. daily. All the patients were asked to take the prescribed amount of the drug once daily, with their breakfast, and to continue the diet they had been following before the trial began. Patients who were taking insulin were started on chlorpropamide, 250 mg. daily and insulin was discontinued after progressively smaller doses for three to four days. Those who were taking other sulfonylureas were changed to chlorpropamide treatment abruptly.

Diabetic control was classified as "good" when postprandial blood sugar was consistently below 150 mg. per 100 ml., as "satisfactory" when consistently between 150 and 200 mg. per 100 ml. and as "unsatisfactory" when above 200 mg. per 100 ml.

Thymol turbidity and serum alkaline phosphatase values were determined and leukocyte counts were done before starting the drug and then approximately once monthly. Urine was tested for glucose, protein and acetone at each visit.

From the Institute for Metabolic Research Highland-Alameda County Hospital, Oakland 6.

Submitted August 22, 1960.

If patients did not keep their appointments, they were reminded by telephone or letter and every effort was made to insure continuity of treatment and supervision.

THE PATIENTS

Seventy-eight patients, 23 men and 55 women, were selected for treatment with chlorpropamide. Their ages varied from 31 to 87 years (mean, 58.3 years) at the time of the study and from 31 to 85 years (mean, 52.5 years) at the time diabetes was diagnosed. Only seven patients were under 40 years of age at the time of the study. The high proportion of patients over 40 years old reflects the predominance of old people receiving county hospital care as well as the increased incidence of this type of diabetes with advancing age. The duration of diabetes varied from three months to 40 years (mean, 5.9 years).

Some patients were overweight and clearly did not follow their prescribed diets. Weights at the beginning of the trial varied from 106 to 256 pounds (mean, 162 pounds).

Forty-four patients had taken insulin at some time. Doses varied from 5 to 90 units daily (mean, 30 units daily). Twenty-nine patients had been treated with tolbutamide and 13 with metahexamide. Seventeen patients had received neither insulin nor a sulfonylurea.

TABLE 1.—*Data on Patients with Primary Failure of Treatment of Diabetes with Chlorpropamide (1 Gm. Daily for at Least One Month)*

Duration of Diabetes (Years)	Age	Response to: Tolbutamide	Response to: Metahexamide	Pre-sulfonylurea Insulin Dose (Units per Day)	Initial Weight (Pounds)	Subsequent Therapy	
8	62	PF	PF	20S	222	Diet only	Unsatisfactory
8	74	SF	PF	....	172	D.B.I. 150 mg. per day	Satisfactory
6	49	....	....	45S	118	D.B.I. 100 mg. per day	Satisfactory
10	54	PF	PF	30S	120	D.B.I. 75 mg. per day	Unsatisfactory
7	57	....	....	20S	146		
9	42	PF	....	....	146	D.B.I. 150 mg. per day plus chlorpropamide 250 mg. per day	Satisfactory
3	67	PF	....	40S	155	D.B.I. 150 mg. per day plus chlorpropamide 250 mg. per day.	Satisfactory
3	66	SF	PF	80S	131	N.P.H. 50 units per day insulin	Satisfactory
Mean: 6:8				39.2	151.2		

PF=Primary failure. SF=Secondary failure. S=Satisfactory control.

TABLE 2.—*Data on Patients with Secondary Failure of Treatment of Diabetes with Chlorpropamide*

Duration of Diabetes (Years)	Response to Tolbutamide	Insulin Dose (Units per Day)	Duration of Chlorpropamide Therapy (Months)	Weight in Pounds: Initial	Weight in Pounds: Final
16	PF	35S	4	128	118
1	....	22S	6	188	186

PF=Primary failure. S=Satisfactory control.

RESULTS

Initial Response. Seventy of the 78 patients maintained postprandial blood sugar levels consistently lower than 200 mg. per 100 ml. Good diabetic control (postprandial blood sugar consistently below 150 mg. per 100 ml.) was achieved in 58 and satisfactory control (postprandial blood sugar between 150 and 200 mg. per 100 ml.) in 12 patients. The eight patients who had postprandial blood sugar greater than 200 mg. per 100 ml. despite a maximum dose of chlorpropamide of 1 gm. daily for at least one month, were classified as showing primary failure of treatment. Details of this group of patients are given in Table 1.

Withdrawals. Six patients, all diabetically well controlled, were taken off chlorpropamide within one month, four because of serious or troublesome side effects, one because of leaving the district and one because the disease could be controlled by diet alone. Ten patients were taken off the drug despite good control for at least three months: Two of them were grossly obese and gained weight, three were controlled by diet alone, one showed a granulocytopenia, one because of development of gastric ulcer, one refused to continue treatment because of headaches which were no more frequent or severe than before starting it, and two defaulted.

Secondary failure, defined as unsatisfactory diabetic control occurring despite a dose of chlorpropamide of 1 gm. daily in the absence of change in the diet or gain of weight and following a period of good or satisfactory control, was seen in two patients (Table 2).

Dose-response Relationships. Data on the relationship of dosage to response for the 70 patients who showed an initial good or satisfactory response to chlorpropamide are shown in Table 3.

Table 4 gives data on the relationship of dosage to the duration of diabetes for the 68 patients who showed sustained good or satisfactory control. The mean duration of diabetes for the patients who responded to chlorpropamide was 6.7 years as compared with a mean duration of 6.8 years for those who showed primary failure to respond.

COMPARISON OF CHLORPROPAMIDE WITH INSULIN AND WITH OTHER SULFONYLUREAS

Thirty-eight patients who maintained good or satisfactory diabetic control on chlorpropamide had previously been treated with insulin. Twenty-nine were well controlled and nine were satisfactorily controlled on chlorpropamide. The mean insulin requirements for the two groups was 28.1 and 32.2 units per day respectively, and the mean chlorpro-

TABLE 3.—*Results of Chlorpropamide Treatment Related to Whether Patient Had Been Previously Treated with Insulin or Sulfonylurea*

Dose in Gm. per Day	Good Control					Satisfactory Control					Total
	0.125	0.25	0.50	0.75	1.0	0.125	0.25	0.50	0.75	1.0	
Previously treated with insulin and/or sulfonylurea	3	21*	13*	4	1	0	2	1	5	3	53
Not previously treated with insulin or sulfonylurea	5	7	3	1	0	0	0	0	1	0	17
Total	8	28*	16*	5	1	0	2	1	6	3	70

*Including one patient who subsequently showed secondary failure.

pamide dosage 0.39 and 0.72 gm. per day. The patients who were well controlled on chlorpropamide had an insulin-to-chlorpropamide equivalence ratio of 72 units to 1 gm., while for those who were satisfactorily controlled the ratio was 32 units to 1 gm. The mean insulin requirement of the patients in the primary failure group was 39.2 units daily.

There are insufficient data in the medical records of many of the 29 patients who had been treated with tolbutamide to calculate a valid chlorpropamide-to-tolbutamide potency ratio, and the 13 patients who had received metahexamide took the drug for too short a time to allow a chlorpropamide-to-metahexamide potency ratio to be determined. The relative responses of 29 patients to chlorpropamide and tolbutamide are shown in Table 5. (In compiling the data, it was assumed that patients who were consistently aglycosuric on tolbutamide were "controlled.")

Effect on Weight. Of the 64 patients who showed good or satisfactory response to chlorpropamide for at least three months, 33 gained weight, 27 lost weight and four showed no change of weight. Change of weight is related to chlorpropamide dosage and duration of treatment in Table 6 for patients whose initial weights were above and below the median of 157 pounds.

Effect on Leukocytes and on Liver Function Tests. There was no change in serial leukocyte counts except in one patient who showed granulocytopenia (total count 2,900 per cu. mm., with neutrophils 33 per cent, lymphocytes 63 per cent, monocytes 2 per cent, eosinophils 1 per cent, basophils 1 per cent) which disappeared when the drug was stopped.

Data are available on serial estimations of thymol turbidity and serum alkaline phosphatase for 56 patients who took chlorpropamide for more than three months. Normal values were considered to be 0 to 4 units for thymol turbidity and 1.5 to 4 units (Bodansky) for serum alkaline phosphatase. The changes recorded were relatively minor and are analyzed in Table 7.

SIDE EFFECTS

Anorexia, nausea and abdominal discomfort were experienced by several patients but were not very troublesome and disappeared within a few days of starting treatment in all but two patients who had to be taken off the drug after one month (0.25 gm. per day) and two weeks (0.5 gm. per day) respectively. One patient was found to have a large gastric ulcer after 16 months on 0.25 gm. daily.

TABLE 4.—*Chlorpropamide Dose Related to Duration of Diabetes in Cases of Sustained Good or Satisfactory Control*

	Mean Dose (Gm. per Day)	Number of Patients
Duration of diabetes:		
1 year	0.26	10
1 to 4 years	0.45	23
5 to 9 years	0.49	17
10 to 14 years	0.47	12
15 to 19 years	0.29	3
20 or more years	0.33	3

TABLE 5.—*Comparison of Response to Chlorpropamide and Tolbutamide*

Response to Tolbutamide	Response to Chlorpropamide		
	Good	Satisfactory	Unsatisfactory
Controlled*	11	4	1
Uncontrolled	5	2	6†

*Consistently aglycosuric.
†Including one patient with secondary failure to tolbutamide.

Rash. One of the first patients treated with chlorpropamide had received 1 gm. daily for two weeks when she had an itchy, maculopapular rash, chiefly on the trunk, a low grade fever and weakness and ataxia. These symptoms disappeared within a few days of discontinuing the drug. She refused to take a smaller dose and resumed insulin treatment.

Jaundice. A woman aged 55 had been a diabetic for 12 years and was well controlled with N.P.H. insulin, 40 units daily. She was transferred to metahexamide 100 mg. daily on March 29, 1959, and to chlorpropamide 750 mg. daily on June 18, 1959. She was admitted to the hospital on July 27, 1959, with complaints of generalized itching, anorexia and lassitude.

The body temperature was 38.9° Centigrade. There was widespread maculopapular rash on the trunk, and the patient was moderately jaundiced. The liver and spleen were impalpable. Packed cell volume was 40 per cent. Leukocytes numbered 11,500 per cu. mm.—neutrophils 62 per cent, lym-

TABLE 6.—*Relationship of Chlorpropamide Dosage and Duration of Treatment to Weight Change*

	Initial Weight More Than 157 Pounds		Initial Weight Less Than 157 Pounds		
	Lost	Gained	Lost	Gained	Unchanged
No. of patients	12	20	15	13	4
Mean initial weight (pounds)	191	185	138	136	129
Mean weight change (pounds per month)	1.08	0.97	0.88	0.87	....
Mean dose (gm. per day)	0.48	0.44	0.49	0.32	0.44
Per cent well controlled	75	75	73	92	75

TABLE 7.—*Changes in Liver Function Tests During Chlorpropamide Treatment*

	No. Pounds	Elevated Before Treatment		Mean Dose Gm. per Day	Duration of Chlorpropamide Therapy (Months)
		T.T.*	A.P.†		
No change in T.T. or A.P.	39	0	0	0.41	9.6
Increase in T.T. only	9	1	0	0.51	10.9
Increase in A.P. only	5	0	2	0.60	12.0
Increase in both T.T. and A.P.	3	1	2	0.79	13.7

*T.T.=Thymol turbidity. †A.P.=Alkaline phosphatase.

phocytes 24 per cent, monocytes 1 per cent, eosinophils 13 per cent. The icterus index was 40 units. Thymol turbidity was 1.2 units. Cephalin-cholesterol flocculation was negative at 48 hours. Alkaline phosphatase was 60 King-Armstrong units. Blood urea nitrogen was 21 mg. per 100 ml. Liver biopsy showed periportal infiltration with round cells and eosinophils, intracanalicular bile stasis and bile staining of some parenchymal cells.

Chlorpropamide was discontinued and the diabetes was controlled with insulin. The rash spread and desquamated. The jaundice subsided within three weeks and the patient was discharged from the hospital on August 20, 1959. Thymol turbidity and alkaline phosphatase were normal and cephalin-cholesterol flocculation negative one month later. Diabetes was well controlled by 40 units of N.P.H. insulin daily.

Hypoglycemia (a manifestation of overdosage rather than a side effect) was probably experienced in a mild form by three patients. Further episodes were prevented by discontinuing the drug in two patients (each taking only 0.125 gm. daily) and by reducing the dose from 0.25 to 0.125 gm. daily in the other.

Alcohol intolerance was seen in one patient when she was taking chlorpropamide 1 gm. daily. She complained of flushing, palpitation and nausea after drinking amounts of whisky which had previously caused none of these symptoms.

DISCUSSION

Chlorpropamide, like the related sulfonylureas, carbutamide and tolbutamide, has little or no hypoglycemic activity in patients with severe, insulin-dependent, juvenile-type diabetes, occurring either spontaneously[13] or after total pancreatectomy.[11] It is useful in the treatment of many patients with mild, noninsulin-dependent, maturity-onset diabetes. Carbutamide which is excreted relatively slowly and gives a steady plasma level when given once daily is no longer used in this country because it has dangerous side effects.[6] Tolbutamide is remarkably safe but has the disadvantage of being excreted so rapidly that multiple daily dosage is usually necessary to maintain therapeutically adequate plasma levels. The plasma half-lives of tolbutamide and chlorpropamide are 5 and 36 hours respectively.[7] When a fixed dose of chlorpropamide is taken once daily the plasma concentration increases for several days (depending on the dose) and then remains steady.[2] Maintenance of a constant plasma level with a single daily dose is convenient for the patient, unless dosage has been excessive, in which case the slow excretion of the drug becomes a disadvantage.

Tolbutamide and chlorpropamide are equally effective in reducing the blood sugar during acute studies in normal subjects or in patients with mild diabetes[3] but when administered for prolonged periods, chlorpropamide is three to six times as potent as tolbutamide[4] because it is excreted more slowly. There is nothing to suggest any qualitative differences between the modes of action of the two drugs. Some patients are unsatisfactorily controlled on tolbutamide but well or satisfactorily controlled on chlorpropamide (Table 5). This is probably due in most instances to the higher and more sustained plasma sulfonylurea levels achieved with chlorpropamide. A pronounced difference in response to the two drugs suggests negligence in taking multiple daily doses of tolbutamide. One of the patients in the better series was better controlled on tolbuta-

mide than chlorpropamide. Unfortunately, plasma sulfonylurea levels are not available for comparison.

It was possible with several of the patients to decrease the dose of chlorpropamide during the trial without deterioration of diabetic control. When this was done the doses, as shown in the tables, are the mean for the period of treatment, excluding the first month. All the patients in the series who responded to chlorpropamide did so promptly and, unlike Lee and coworkers[8] we did not observe delayed responses such as have been reported with tolbutamide by Walker and coworkers.[15]

It is difficult to assess the significance of changes in weight during the trial. Table 6 shows no relationship to initial weight, to chlorpropamide dosage or to duration of treatment. Although all the patients were asked not to change their diet, some undoubtedly followed their prescribed diets more faithfully when seen so frequently, while others undoubtedly ate more than they should have when they became aglycosuric.

There is no difference in the duration of diabetes in the groups of patients who responded well or satisfactorily and those who showed primary failure to respond. Table 4 shows that patients with diabetes of less than one year duration required less chlorpropamide than the remainder of the patients, with the exception of those who had been diabetic for more than 15 years. The mean age of these latter patients was 66.7 years, compared with 58.3 years for the series as a whole. There is a suggestion of some correlation between previous insulin dosage and response to chlorpropamide. The mean insulin dose was 28 units per day for the patients who were well controlled on chlorpropamide, 32 units per day for those who were satisfactorily controlled and 39 units per day for those who showed primary failure.

The high incidence of side effects, particularly of anorexia, nausea, abdominal discomfort and rashes noted in the early reports on chlorpropamide was due to excessive dosage. Only two of the 78 patients in the present series were unable to tolerate the drug because of abdominal symptoms and one (excluding the patient who also became jaundiced) developed a rash (after taking 1 gm. daily for two weeks).

One of our patients showed granulocytopenia which disappeared when chlorpropamide was stopped. Similar instances have been mentioned by Reyes and coworkers.[13]

Intrahepatic cholestatic jaundice occurred in one of the patients and was probably due to chlorpropamide, although she had taken metahexamide for two months and was transferred to chlorpropamide six weeks before the jaundice appeared. The onset within six weeks of starting the drug and the association with a maculopapular rash are characteristic. Increased serum alkaline phosphatase with little or no change in the flocculation liver function tests, and liver biopsies which show cholestasis and round cell infiltration of the portal areas, indicate an obstructive process. Reduction of prothrombin activity with poor response to vitamin K injections in some cases shows that hepatocellular damage also occurs. Reichel and coworkers[12] expressed belief that this type of jaundice is a result of hypersensitivity to the drug such as is seen with chlorpromazine. They estimated its incidence as approximately 0.5 per cent. Hamff and coworkers[5] were able to resume treatment without recurrence of the jaundice or other symptoms or deterioration of liver function tests in two of three patients who had recovered from chlorpropamide jaundice.

Most of the early reports on relatively short term studies stated that chlorpropamide treatment was not associated with any change in liver function tests, but Burrell[1] mentioned that he had seen transient abnormalities in the thymol turbidity test in 12 of 130 patients who received the drug for one to thirteen months (mean 6.3 months). In the present series the 56 patients for whom we have serial liver function tests were treated for from three to twenty-four months (mean 10.2 months). Thirty-nine showed no change of either thymol turbidity or serum alkaline phosphatase, eight showed an increase of thymol turbidity from the normal range to above the upper limit of normal, five showed a similar increase of serum alkaline phosphatase and one patient with normal baseline values showed an increase beyond the upper limits of normal of both thymol turbidity and serum alkaline phosphatase. Table 7 shows that patients with changes in liver function tests took more chlorpropamide and for longer than those who showed no change and that all of the six patients who showed minor abnormalities of liver function by these tests before treatment showed deterioration during treatment. These observations suggest that further and more detailed studies of the effect of long-term chlorpropamide administration on liver function are indicated.

Three of the patients in this series probably became mildly hypoglycemic. Symptoms were mild, were relieved by food and were abolished by stopping treatment in two cases and by reducing the dose in the other case. We have not seen severe and persistent hypoglycemia after moderate dosage as reported by Lindeman and coworkers.[9]

One of the patients was unable to tolerate alcohol while she was taking 1 gm. of chlorpropamide daily. Chlorpropamide-induced alcohol intolerance has been mentioned by several observers and described in detail by Signorelli and coworkers.[14] The effects resemble those of disulfiram (Antabuse). The mechanism is unknown.

It is the opinion of the authors that chlorpropamide is a highly useful drug. If dosage in excess of 0.5 gm. per day is required, liver and hematologic indices should be checked at intervals during the first year of such treatment.

ACKNOWLEDGMENT

We wish to thank Dr. D. G. Iezzoni of Pfizer Laboratories for generous supplies of chlorpropamide.

Institute for Metabolic Research, Highland-Alameda County Hospital, 2701 Fourteenth Avenue, Oakland 6 (Kinsell).

REFERENCES

1. Burrell, Z. L., Martinez, A., and Burrell, L. O.: One year of clinical experience with chlorpropamide in more than one hundred diabetic patients, Ann. N. Y. Acad. Sci., 74:696, 1959.

2. Carlozzi, M., Iezzoni, D. G., and Silver, L.: Blood levels of chlorpropamide in normal men following chronic administration, Ann. N. Y. Acad. Sci., 74:788, 1959.

3. Craig, J. W., Miller, M., Mills, F. D., and Nickerson, N.: A comparison of the acute hypoglycemic potencies of tolbutamide and chlorpropamide, Ann. N. Y. Acad. Sci., 74:618, 1959.

4. Forsham, P. H., Magid, G. J., and Dorosin, D. E.: A clinical comparison of chlorpropamide and tolbutamide, Ann. N. Y. Acad. Sci., 74:672, 1959.

5. Hamff, L. H., Ferris, H. A., Evans, E. C., and Whiteman, H. W.: The effects of tolbutamide and chlorpropamide on patients exhibiting jaundice as a result of previous chlorpropamide therapy, Ann. N. Y. Acad. Sci., 74:820, 1959.

6. Kirtley, W. R.: Occurrence of sensitivity and side reactions following carbutamide, Diabetes, 6:72, 1957.

7. Knauff, R. E., Fajans, S. S., Ramirez, E., and Conn, J. W.: Metabolic studies of chlorpropamide in normal men and in diabetic subjects, Ann. N. Y. Acad. Sci., 74:603, 1959.

8. Lee, C. T., Schless, G. L., and Duncan, G. G.: Clinical experiences with chlorpropamide: A double-blind study, Ann. N. Y. Acad. Sci., 74:738, 1959.

9. Lindeman, R. D.: Severe hypoglycemia caused by chlorpropamide, Diabetes, 9:110, 1960.

10. McLamore, W. M., Fanelli, G. M., P'an, S. Y., and Laubach, G. D.: Hypoglycemic sulfonylureas: Effects of structure on activity, Ann. N. Y. Acad. Sci., 74:443, 1959.

11. Pines, K. L., Leifer, E., and Goodman, D.: Influence of chlorpropamide upon postpancreatectomy and spontaneous diabetes, Ann. N. Y. Acad. Sci., 74:997, 1959.

12. Reichel, J., Goldberg, S. B., Ellenberg, M., and Schaffner, F.: Intrahepatic cholestasis following administration of chlorpropamide, Am. J. Med., 28:654, 1960.

13. Reyes, J. A. G., Pena, J. C., Barroso, E., Anton, F. B. S., and Gonzales, C.: Clinical experience in the use of chlorpropamide in the treatment of diabetes mellitus, Ann. N. Y. Acad. Sci., 74:1012, 1959.

14. Signorelli, S.: Tolerance for alcohol in patients on chlorpropamide, Ann. N. Y. Acad. Sci., 74:900, 1959.

15. Walker, G., Slater, J. D. H., Westlake, E. K., and Nabarro, J. D. N.: Clinical experience with tolbutamide, Brit. Med. J., 1:323, 1957.